Journal of Surgical Oncology 62:115–122 (1996)

Postoperative Recurrence of Solitary Small Hepatocellular Carcinoma

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The prognosis of hepatocellular carcinoma after hepatic resection remains poor. The major cause is postoperative recurrence, most frequently intrahepatic. During the past 7 years, we conducted a detailed study of recurrence after hepatectomy in 34 patients with solitary small hepatocellular carcinoma measuring no larger than 4 cm in diameter, in which 13 cases had postoperative recurrent tumors, and two cases were considered multicentric. Eighty-five percent of recurrences were diagnosed at 6–18 months after the operation. The cumulative recurrence rates were 61% at 5 years after operation. When analyzing the factors affecting recurrence, a significant difference was observed regarding tumor diameter. After recurrence, most patients underwent percutaneous ethanol injection treatment and/or transcatheter arterial chemoembolization and lipiodolization. Four patients died of progressive disease within 1 year after recurrence; the treatment thus seemed to have no effect. The other patients with recurrence remain alive with the disease. The overall cumulative survival rates in this series were 76% at 3 years and 60% at 5 years after operation. To obtain better results after hepatectomy, even for small hepatocellular carcinoma, careful, long-term follow-up evaluation is therefore necessary for the multidisciplinary treatment of the postoperative recurrence, as well as the early diagnosis of tumors in high-risk patients.

KEY WORDS: **hepatocellular carcinoma, hepatic resection, postoperative recurrence**

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most malignant tumors. In spite of recent advances in imaging modalities in combination with a strict follow-up of high-risk patients and liver surgery, the outcome remains poor. Short-term results have certainly improved, because of better surgical techniques, and the operative mortality rates have also decreased [1]. The long-term results are not yet satisfactory, however, primarily because of the high rate of postoperative recurrence. The postoperative recurrence of HCC remains the major cause of death and the main obstacle to long-term survival. Several reports have been published regarding the postoperative recurrence of HCC [2–6]. However, little is known about the details of small HCC and the subsequent clinical course. It would therefore be most useful to know the real nature of the postoperative recurrence of HCC. We present a detailed analysis of recurrence after hepatic resection for solitary small HCC and of several factors affecting recurrence, as well as discussing various treatment options.

PATIENTS AND METHODS

Between March 1988 and January 1995, we performed a hepatic resection for HCC on 91 patients. All patients were routinely examined by conventional ultrasonography (US), dynamic computed tomography (CT) with contrast medium, and hepatic angiography (HA). Of these, 34 had a solitary HCC, not larger than 4 cm in diameter. We sometimes encountered HCC with small intrahepatic metastasis during and/or after the operation using intraop-

Accepted for publication February 20, 1996.
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TABLE I. Clinical Features of 34 Patients With Solitary Small Hepatocellular Carcinoma

Data	No. of cases	%
Sex		
Male	27	79.4
Female	7	20.6
Positive HBs-Ag level[a]	5	14.7
Positive HCV-Ab level[b]	24	70.6
Liver cirrhosis	21	61.8
Tumor size		
≤2 cm	14	41.2
Child's classification		
A	27	79.4
B	6	17.6
C	1	3.0

[a]HBs-Ag, hepatitis B surface antigen.
[b]HCV-Ab, hepatitis C antibody.

erative US and a cross-sectional examination of the dissected specimen, preoperatively diagnosed as solitary HCC. However, such cases were excluded, and only the 34 solitary HCCs were investigated. All cases were histologically proven except for two cases, whose tumors showed complete necrosis after preoperatively undergoing either transcatheter arterial chemoembolization (TAE) [7] or lipiodolization [8]. These two cases were diagnosed as HCC based on imaging modality findings before treatment.

Most of the tumors were asymptomatic and discovered during surveillance by US and/or after measuring the serum α-fetoprotein (AFP) level. An AFP level of >400 ng/ml was recognized in 6 of 34 patients (18%).

The clinicopathological features are given in Table I. Hepatitis B surface (HBs) antigen was positive in 5 patients, while hepatitis C virus (HCV) antibody was positive in 24, based on an examination at first admission before operation. Liver cirrhosis was histologically recognized in 21 patients. A partial resection of less than one segment was performed in 27 patients, a resection of not more than two segments was done in five patients, and two patients underwent a hepatic lobectomy. The eight segments of the liver are described based on the criteria of Couinaud [9]. All had a curative operation. One patient died within 1 month after operation (operative death). Therefore, 33 patients in all were analyzed regarding recurrence.

Pathological Examination

The resected specimens were cut into serial slices measuring <10 mm thick. When the surgical margin was <10 mm in the resected specimen, it was determined to be tumor wedge (TW) positive; while when it was 10 mm or more, it was then considered to be TW negative.

After macroscopic observation, all specimens were fixed in 10% formalin, and the slices with the largest diameter were trimmed for paraffin blocks. The blocks were cut into 5-μm microscopic sections and stained with hematoxylin and eosin (H&E) for histological examinations to determine the fibrous capsular formation of the tumor (fc), intracapsular infiltration (fci) and tumor invasion into the portal vein (pvi) [5].

Follow-Up Evaluation

After discharge, periodic surveillance was carried out by measuring the serum AFP level and imaging using such modalities as US, CT, and, when necessary, HA. In most cases, US was done once every 2–3 months, while CT was done once every 6–12 months. HA was performed only when the recurrence was either strongly suspected or proven by using US, CT, and TAE, or lipidolization was planned.

Recurrence of HCC is fundamentally based on a histological diagnosis by either a US-guided tumor biopsy or an analysis of a surgically resected specimen. However, HCC is often complicated with such chronic liver diseases as chronic hepatitis or liver cirrhosis and it is sometimes too dangerous to obtain a tumor specimen. However, thanks to recent advances in imaging modalities, with the combined use of US, CT, and HA, an accurate diagnosis of HCC can now almost always be made. In addition, an examination of the HBs antigen, HCV antibody and AFP level is also useful. Recurrence can also be diagnosed when the following findings are demonstrated: increase in tumor size on US or CT; an early increase and rapid decline in the contrast enhancement in dynamic CT [10]; or the presence of arterial neovasculature as shown by HA.

When the recurrent tumor is around 2 cm in diameter and the total number of tumors is less than four, percutaneous ethanol injection treatment (PEIT) [11] is usually performed. In most cases, 3–5 ml of ethanol is injected not only into the center of the tumor, but also into sites close to the edge. Otherwise, using the Seldinger's method [12], iodized oil contrast medium, Lipiodol (Laboratoire Guerbet S.A., Paris), mixed with 30–20 mg of epirubicin (Pharmacia, Milan) and 10 mg of mitomycin C (Kyowa Hakko Kogyo Co., Tokyo), was injected, in the early days of this series, followed soon thereafter by an injection of gelatin sponge cut into small pieces in the hepatic artery. More recently, 50 mg of epirubicin has been administered. In addition, when the liver function of the patients was poor, lipiodolization without an injection of gelatin sponge was performed. TAE or lipiodolization, using smaller doses of antitumor agent than used after recurrence, was performed before hepatectomy in 6 of 33 patients as a preoperative treatment.

Statistical Analysis

The results are expressed as the mean ±SD. The survival rates and cumulative recurrence rates after operation

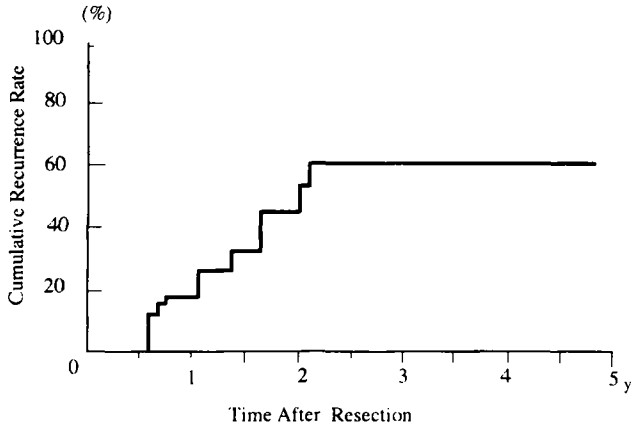

Fig. 1. Cumulative recurrent rates of hepatocellular carcinoma.

were calculated using the Kaplan–Meier method [13]. The chi-square test was used with Yates' correction factor [14]. Differences were considered statistically significant at $P < 0.05$.

RESULTS

The follow-up period ranged from 5 months to 6 years and 6 months (25 ± 18.5 months); 13 of the 33 patients had postoperative recurrence. Of the 13 recurrent cases, three cases (23%) were histologically proven. All others were considered to be recurrence based on the US, CT, and HA findings. Five patients (38%) died due to tumor growth, one of whom died from bone metastasis. Eighty-five percent of recurrences were diagnosed between 6 months and $1\frac{1}{2}$ years after resection. The shortest diagnosed instance of recurrence was 6 months and the longest was 5 years. The cumulative recurrent rates were 18% at 1 year, 53% at 2 years, 61% at 3 years, and 61% at 5 years after operation, respectively (Fig. 1). The follow-up details of the recurrence are shown in Figures 2, 3, and 4. The recurrent tumor diameter measured around 2–3 cm at the first detection. All observed recurrences were of the nodular type, while no instances of either multiple or diffuse types were seen. Two cases were considered multicentric, and one synchronous (case 6), while the another was metachronous (case 1).

The details of the clinicopathological data for the recurrent cases are shown in Table II. Eight of the 13 were patients with cirrhosis of the liver. A positive TW was seen in 8 cases. Case 4 was TW negative based on the postoperative findings. In case 12, no portal vein invasion was recognized by microscopic examination, but bile duct invasion was identified.

Two patients showed extrahepatic metastasis, with one demonstrating bone metastasis, found after intrahepatic recurrence (case 13), while the other had a mediastinal tumor without intrahepatic metastasis (case 8). Most recurrent cases were treated with PEIT, TAE, and lipiodolization. Although four patients died due to disease progression within 1 year after recurrence, in spite of undergoing treatment, many patients with recurrences have remained alive with the disease. The overall postoperative cumulative survival rates in the 33 patients with HCC in this series over the past 7 years were 96% at 1 year, 76% at 3 years, and 60% at 5 years, respectively (Fig. 5). Sample cases are presented below.

Case Reports

Case 3. A 62-year-old man had previously undergone a partial hepatectomy because of HCC measuring 1.2 cm in diameter in segment VIII. The noncancerous liver parenchyma showed liver cirrhosis. His HBs antigen serum was negative, while his HCV antibody was unknown. At operation, his liver function was Child B [15]. During the follow-up period, a 2.0-cm mass was recognized around segments VI–VII at 6 months after operation, which was determined to be nodular recurrence. Ten months after the operation, the mass remained the same size, but a new smaller mass later appeared in segment VII. Three years after the operation, after lipiodolization, the tumor in segment VII decreased in size from 3.2 to 2 cm in diameter, while the mass in segment VI showed no change in size. At present, after undergoing interventional angiography three times in total, 5 years after the operation, he is still alive with the disease.

Case 4. A male patient underwent a colon cancer operation 8 months after a first hepatic resection of an HCC measuring 1.2 cm in diameter. The colon cancer was histologically found to be adenocarcinoma. One year and 4 months after hepatectomy, small nodules of measuring about 1 cm in size were recognized in segments III and V. During the follow-up, the tumor in segment V disappeared, while the other tumor in segment III gradually increased in size. Four years after the first operation, a left lateral segmentectomy (a resection of segments II and III) was performed for the 2-cm nodule in segment III. The histological diagnosis was not HCC, but adenocarcinoma, which was compatible with colon metastasis. Thereafter, a nodule measuring about 2 cm in size was detected in segment V, which was diagnosed as HCC based on the US, CT, and HA findings. Following treatment, the patient has since demonstrated no further clinical symptoms in spite of the presence of small tumors.

Case 5. A male patient demonstrated a marginal recurrence after a partial hepatectomy for an HCC measuring 2 cm in segment VIII. Since then, two small nodules measuring 1.2 cm in segment VII and 2.1 cm in segment VIII were recognized. After treatment, a tumor measuring 4 cm in size still remains in segment VIII while the other nodules seem to have disappeared at present.

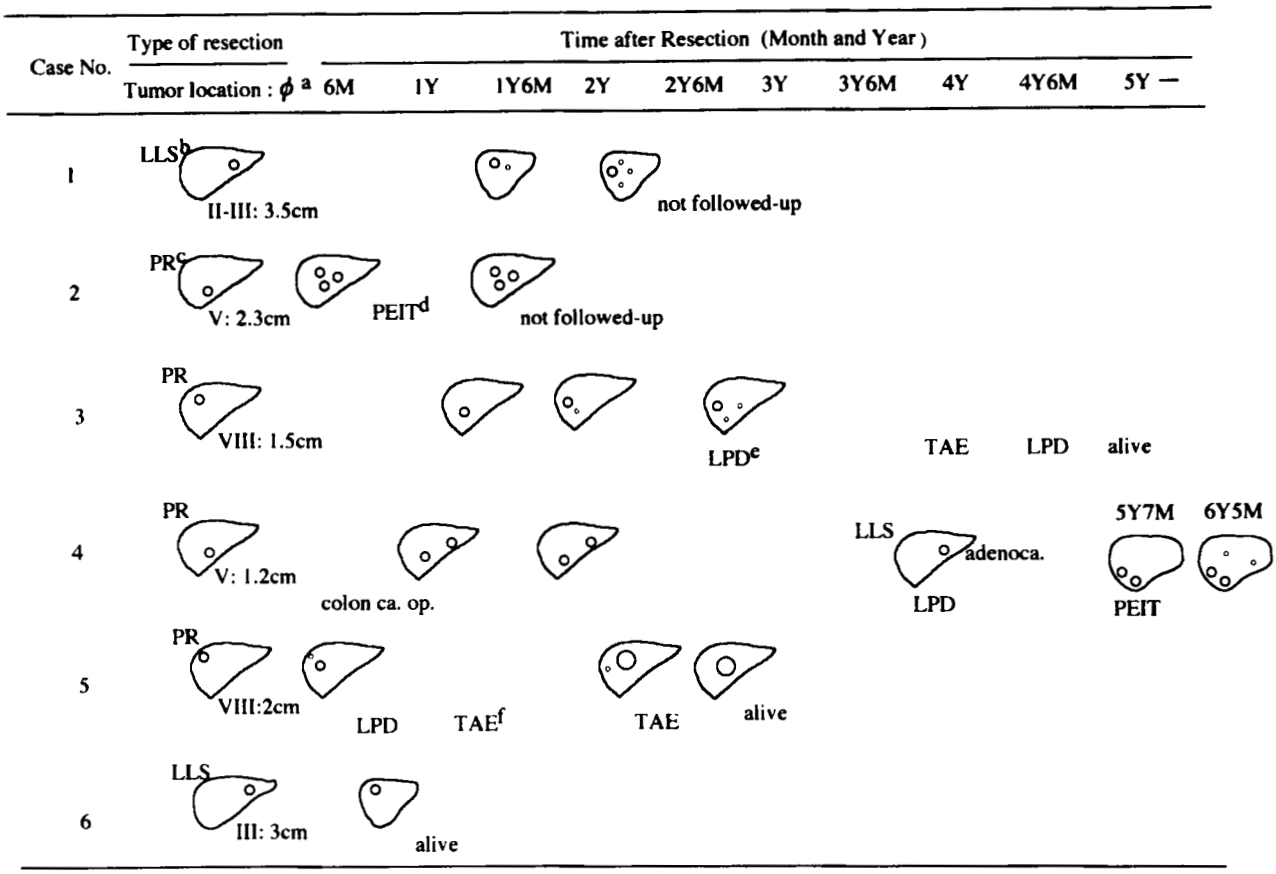

Fig. 2. Details of 13 recurrent cases of hepatocellular carcinoma (cases 1–6). [a]ϕ, maximum diameter of the tumor; [b]LLS, lt. lateral segmentectomy: resection of segment II and III; [c]PR, partial resection; [d]PEIT, percutaneous ethanol injection treatment; [e]LPD, lipiodolization; [f]TAE, transcatheter chemoembolization.

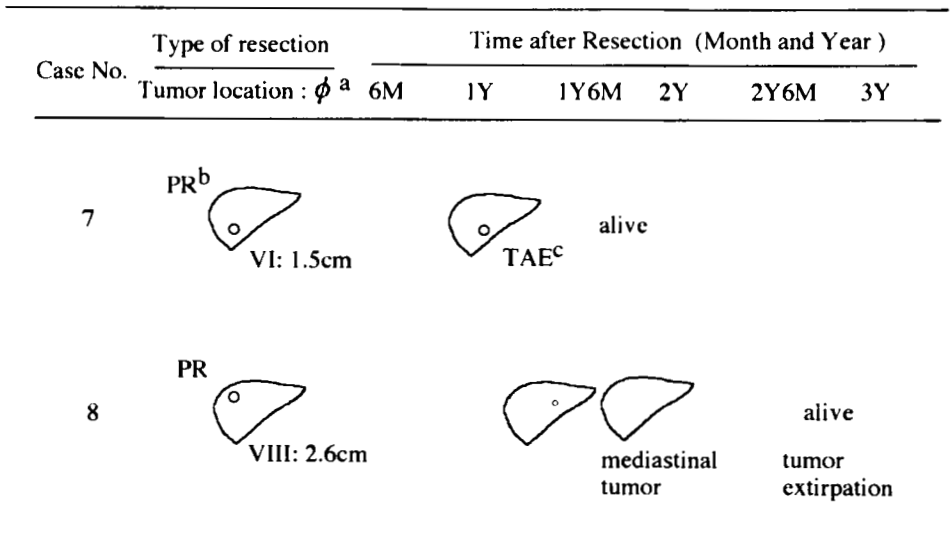

Fig. 3. Details of 13 recurrent cases of hepatocellular carcinoma (cases 7 and 8). [a]ϕ, maximum diameter of the tumor; [b]PR, partial resection; [c]TAE: transcatheter chemoembolization.

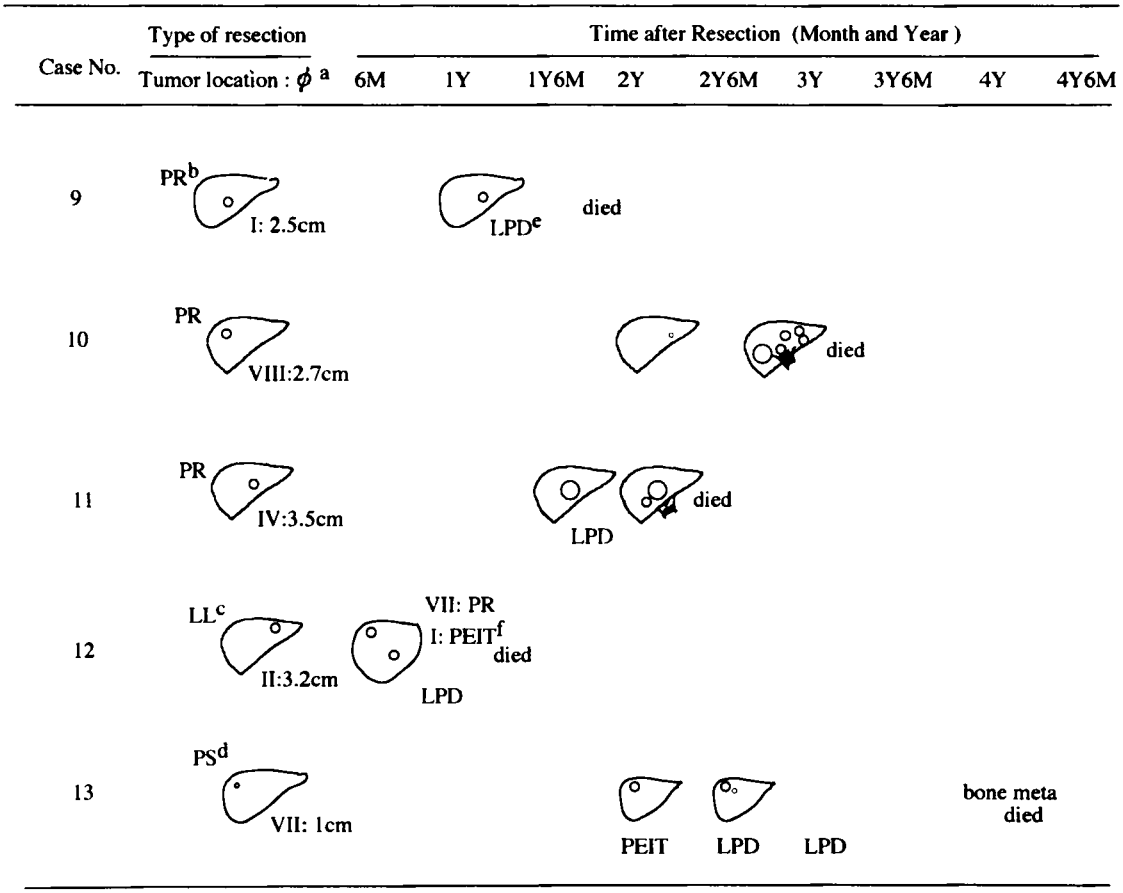

Fig. 4. Details of 13 cases of recurrent hepatocellular carcinoma (cases 9–13). [a]ϕ, maximum diameter of the tumor; [b]PR, partial resection; [c]LL, left lobectomy; [d]PS, posterior segmentectomy: resection of segment VI and VII; [e]LPD, lipiodolization; [f]PEIT, percutaneous ethanol injection treatment.

TABLE II. Clinicopathological Data of 13 Recurrent Cases of Hepatocellular Carcinoma*

Case no.	Tumor location	Diameter (cm)	HBs-Ag	HCV-Ab	Cirrhosis	TW (cm)	pvi	fc	fci
1	III	3.3	−	Unknown	−	0.7	+	−	−
2	V	2.3	+	−	+	0.2	+	+	+
3	VIII	1.2	−	Unknown	+	Unknown	+	−	−
4	V	1.2	−	−	−	−	−	−	−
5	VIII	2	−	+	+	0.4	−	+	+
6	III	3	−	+	+	1.5	−	+	+
7	VI	1.5	−	+	−	1	−	−	−
8	VIII	2.6	−	+	+	0.3	−	+	+
9	I	2.5	−	+	+	0.1	−	+	−
10	VIII	2.7	+	−	+	0.1	−	−	−
11	IV	3.5	−	+	+	0	+	+	+
12	II	3.2	−	+	−	0.7	−	+	+
13	VII	1	−	Unknown	−	Unknown	Bile duct invasion	−	−

*HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; TW, tumor wedge; pvi, tumor invasion into the portal vein; fc, fibrous capsular formation of the tumor; fci, intracapsular infiltration.

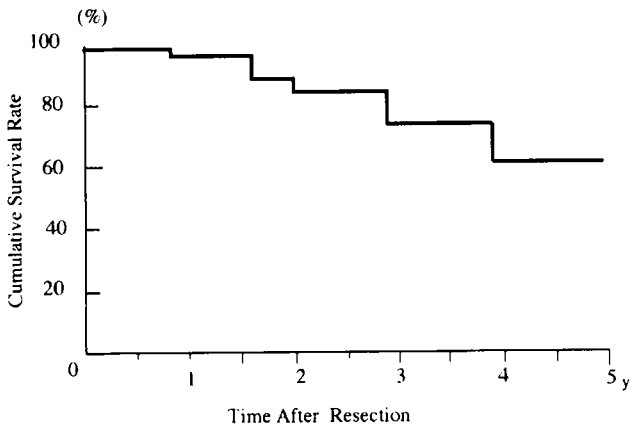

Fig. 5. Overall cumulative survival rates in the 33 patients with hepatocellular carcinoma.

TABLE III. Risk Factors for Recurrence of Hepatocellular Carcinoma After Hepatectomy

Variables		Recurrence Yes	Recurrence No	*P*
Diameter	≦2cm	5	8	<0.05
	>2cm ≦4cm	9	11	
TW	(+)	9	13	N.S.
	(−)	2	6	
fc	(+)	7	16	N.S.
	(−)	7	3	
fci	(+)	6	13	N.S.
	(−)	8	6	
pvi	(+)	5	1	N.S.
	(−)	9	18	
Cirrhosis	(+)	8	12	N.S.
	(−)	6	7	

TW, tumor wedge; fc, fibrous capsular formation of the tumor; fci, intracapsular infiltration; pvi, tumor invasion into the portal vein; N.S., not significant.

Case 6. A female patient demonstrated a 2-cm recurrent tumor in segment VIII, which was considered to have a synchronous multicentric occurrence, within half a year after a resection of segments II and III.

Case 7. A 60-year-old man underwent a partial hepatectomy for an HCC, measuring 1.5 cm in diameter, in segment VI. His serum of HBs antigen was negative but HCV antibody was positive. The resected specimen showed no tumor capsule and no venous invasion. The noncancerous parenchyma did not show liver cirrhosis. A 1-cm TW was observed. One year after the operation, a mass was recognized in segment V. TAE was performed and he remains alive with the disease.

Case 9. A male patient underwent a partial hepatectomy for a 2.5-cm HCC in segment I. After recurrence, he was treated with lipiodolization but died due to liver failure 1 year and 7 months after the operation.

Cases 10, 11, 12. All died within 1 year after recurrence was recognized and two of them had tumor thrombus in the portal vein.

Case 11. This 42-year-old man underwent a partial hepatic resection with no surgical resection margin for a 3.5-cm HCC in segment IV. His serum of HBs antigen was negative but HCV antibody was positive. Histologically, the resected specimen showed microscopic venous invasion and capsule invasion. The noncancerous part of the hepatic parenchyma showed liver cirrhosis. One year and 4 months after the operation, a small mass was suspected using US. Two months thereafter, a 5-cm tumor was recognized in the central liver by US, CT, and HA, and as a result, lipiodolization was performed. However, 2 months later, portal thrombus was recognized and 1 year and 11 months after the operation he died of HCC.

Case 13. This patient had a recurrent tumor measuring 2 cm in diameter in segment VII after hepatectomy (segments VI and VII). Four years after the operation, following one PEIT and two lipiodolization, he died of bone metastasis.

Factors Contributing to Recurrence

A comparison of some factors was made between the recurrence and the no recurrence group (Table III). The significance of such factors was evaluated regarding tumor diameter, surgical resection margin, fc, fci, pvi, and concomitant cirrhosis. Microscopically, bile duct invasion was included into positive pvi. As a result, a significant difference was observed in the tumor diameter between the recurrence group and the no recurrence group.

DISCUSSION

In this series, a histological diagnosis of recurrence was made in only 23% of the cases while the remaining diagnoses were made based on the imaging findings and the clinical course. Many reports regarding the recurrence to date have been based on similar findings [2–6]. However, the recent advances in imaging modalities have been remarkable and the diagnosis of HCC of no larger than 3 cm in diameter have been reported to be more than 80% using US, CT, and HA. Using lipiodol CT, the rate was more than 90% [16]. In addition, when considering that HCC may possibly be complicated by chronic liver disease, hepatitis virus and/or gradual increase of the AFP level, the rate may even be higher.

In the present study, 13 out of 33 (36%) cases had recurrence. This figure is not necessarily high compared with other reports to date. Lin et al. reported, based on their 31-year experience that in 119 of 209 (57%) hepatectomized patients, local recurrence was observed within 1 year after hepatic resection [2]. In a study of 14 Chinese patients with solitary small HCC not larger than 2 cm, five patients (36%) had recurrence [17]. Significantly, in

our series, 11 of 13 (85%) recurred within 18 months of hepatectomy. In other words, postoperative intrahepatic recurrence rarely occurs later than 18 months following hepatectomy for solitary small HCC.

Based on the above findings, the cause of the recurrence after surgical resection of small HCC remains unknown. It might be due to the surgical resection margin or the degree of tumor dispersal during hepatectomy. There might also be tumor thrombi that are not yet detectable with the present imaging modalities in widespread multinodular recurrence in the liver remnant, which was not recognized in the present series. Portal vein invasion, which is present before the operation and/or disseminated during operation from a primary tumor, may thus be the most important and significant factor related to early recurrence in the liver remnant. In addition, the problem of multicentricity also remains. In our study, this rate was 2/13 (15%).

In a report on the natural history of HCC smaller than 3 cm complicating liver cirrhosis, using US, various rates of tumor growth when the mass was about 2 cm were divided into slow (doubling time >8 months), intermediate (doubling time 3–8 months), and rapid (doubling time <3 months) [18]. From another report, the median detectable subclinical period of HCC was deduced to be 3.2 years [19]. Therefore, when a tumor is macroscopically resected out and cancer cells are microscopically left, it seems to take at least a year to grow and be detected by imaging modalities. In addition, the immunological status should also be considered after a surgical resection is performed. Even with the above reports, it is difficult to determine whether tumors recognized after hepatectomy resulted from the original tumor or represent a multicentric origin.

Certainly, we can microscopically find portal invasion even in small HCCs but not so many as in large HCCs. In our present study, there was no statistically significant difference in vessel invasion, capsule formation or capsule invasion, which also seemed to affect recurrence. Tumor diameter was the only factor affecting recurrence.

There are usually three patterns of postoperative recurrence; (1) recurrence near the resected hepatic stump; (2) nodular recurrence: solitary or a few nodules in the other segments away from the resected margin; (3) widespread multinodular recurrence in the liver remnant [4]. The most frequent pattern is said to be local recurrence, which means recurrence near the resected stump. It sometimes includes nodular or marginal patterns. The multinodular type is rare. In the present study, no such type was recognized. This is probably because our series dealt with solitary small HCC, not larger than 4 cm. Many of the reported HCCs reported were advanced large ones, not small asymptomatic ones. Such tumors are naturally considered to recur because of an insufficient surgical resection margin or tumor spread via the portal vein during hepatic resection.

During the follow-up of the patients after hepatectomy, we sometimes noticed that small tumors disappeared, particularly when a US examination was performed. The reason for this remains unclear because a biopsy specimen was not always taken. It might be due to a regenerating nodule in the cirrhotic liver. Similar negative findings were also observed in HA. Although this examination was generally done following positive examination of US, small tumors sometimes could not be shown as a vascular mass. Sonoda et al. [20] reported that small well-differentiated HCC can not be detected angiographically. In the present series, this was observed in cases 2, 3, 13 at the first angiogram.

Therefore, in order to detect recurrent tumors, US and CT are thought to be more useful than measuring the serum AFP level. Serum AFP levels are said to be frequently normal during the early stage of HCC [21]. In our present study, as well, the serum AFP levels of all the recurrent cases were within the normal range when recurrence was first detected (unpublished data). An increase in tumor size was reported not to be necessarily be accompanied by an increase in serum AFP level [22].

It has been generally accepted that a hepatic resection is the best treatment for small HCC arising in cirrhotic patients [23–25]. The results of liver surgery for HCC have markedly changed over the last decade. However, recently developed nonsurgical treatments such as PEIT, TAE, and lipiodolization have also produced good results [8,26,27]. These nonsurgical treatments thus appear to sometimes be more advantageous than surgical treatment because of the great improvements in their effectiveness over the past 5 years.

Based on our findings, the tumor diameter is considered an important factor for obtaining good results after surgical treatment for solitary small HCC. This is the only finding that can be clarified before the surgery. In addition, most recurrent cases these days have remained alive with the disease because of the early multidisciplinary treatment. Therefore, it is necessary to diagnose and treat small HCC. To get better results after hepatectomy even for small HCC, a careful, long-term follow-up is necessary for the multidisciplinary treatment of postoperative recurrence, as well as for the early diagnosis of tumors in high-risk patients.

CONCLUSIONS

During the past 7 years, the data on 34 patients with a solitary, small hepatocellular carcinoma, not larger than 4 cm in diameter, were analyzed with respect to postoperative recurrence. Thirteen cases had a postoperative recurrent tumor. Eighty-five percent of the recurrences were diagnosed from 6 to 18 months after operation. After analyzing the various factors considered to affect recurrence, a significant difference was observed in tumor diameter. After recurrence, most of the patients underwent

percutaneous ethanol injection treatment and/or transcatheter arterial chemoembolization and lipiodolization. Four cases died of progressive disease within 1 year after recurrence and thus this treatment seemed to have no substantial effect. The other recent patients with recurrence remain alive with the disease. Therefore, to obtain better results after hepatectomy, even for small hepatocellular carcinoma, a careful, long-term follow-up is necessary for the multidisciplinary treatment of the postoperative recurrence, as well as the early diagnosis of tumors in high-risk patients.

ACKNOWLEDGMENTS

The authors are grateful to Professor Masazumi Tsuneyoshi for his helpful criticism.

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